VESICULAR EXANTHEMA OF SWINE[1]

STEWART H. MADIN AND JACOB TRAUM[2]

Department of Bacteriology, Berkeley, School of Veterinary Medicine, Davis, University of California

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INTRODUCTION

Vesicular exanthema is an acute, febrile, infectious viral disease of swine, characterized by the formation of vesicles on one or more parts of the body. The parts most commonly affected are the snout, lips, tongue, oral cavity, sole, interdigital spaces, and the coronary band of the foot. Occasionally the udder and teats of nursing sows become involved. Occult cases are occasionally encountered.

The course of the disease is usually about 1–2 weeks, the mortality is less than 5 per cent, and recovery following uncomplicated virus infection is complete. The incubation period in both the natural and experimental disease usually varies from 24 to 72 hours, with extremes ranging from 12 hours to 12 days. All ages as well as all breeds of swine appear to be susceptible.

Vesicular exanthema is of great economic importance since the disease causes serious weight losses in fat hogs, slow gains in feeder stock, deaths in suckling pigs, abortions in pregnant sows, and impaired lactation in nursing sows. In addition, this condition is clinically indistinguishable from foot-and-mouth disease and vesicular stomatitis in swine, thus requiring expensive quarantine procedures.

The natural disease has been reported only within the United States.

HISTORY

On April 23, 1932, a disease afflicting only swine and clinically indistinguishable from foot-and-mouth disease was reported on a ranch near Buena Park, Orange County, California. Quarantine and inspection of the entire area was immediately instituted by State and Federal authorities. On April 28, two additional ranches near the original focus of infection were found to harbor infected swine. Routine inspection on April 30 showed that the disease was also present in Bellflower, Los Angeles County, on two adjoining ranches, some 15 miles distant from the Buena Park foci. By May 4, the disease had spread to a third neighboring ranch, and this was the extent of the infection as it appeared in Los Angeles County. The infection was then discovered on a ranch located about 2 miles north of the original Buena Park focus on May 3, thus ending the spread of infection in Orange County. Inspection of a ranch in San Bernardino County on May 5 and 6 showed the disease to be present although separated by 40–50 miles from the other two foci. The San Bernardino County infection was the last to be reported and represents the extent of the 1932 outbreak. The disease was diagnosed as foot-and-mouth disease, and all animals directly and indirectly involved in the outbreak were slaughtered and buried, the premises washed with lye solution, and all livestock was excluded for 30 days. Indemnities of $203,328

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[2] Present address: United States Department of Agriculture, Plum Island Animal Disease Laboratory, Greenport, Long Island, New York.

for the loss of the 18,747 swine, 46 cattle and 24 goats were paid jointly by the State of California and the Federal Government (1, 2).

The virus from the 1932 outbreak failed to induce lesions in 24 guinea pigs, 2 calves, 2 heifers, 1 adult cow, and 2 horses (3). On the basis of these tests the diagnosis of foot-and-mouth disease was made even though Traum (4) recognized that it was rather atypical. All virus collected during the outbreak was ordered destroyed.

In March of 1933, a disease again restricted to swine and clinically similar to the 1932 outbreak appeared in San Diego County, California, 100 miles distant from the 1932 foci. The original focus and the immediately adjoining ranch were both found to be infected on March 20, and the infection was reported from a third ranch on March 31 and at a fourth ranch a few days later (Traum, personal observation). Virus from this outbreak was collected and tested in a variety of animals. Infection was established in all of 15 swine, in 4 of 9 horses, but in none of 7 cattle and none of 37 guinea pigs (3).

Similar results on a larger number of animals were obtained by Mohler (private communication) and Reppin and Pyl (5). Observers of the animal tests, with experience in foot-and-mouth disease, saw no definite points of clinical difference between that disease in swine and the one produced by the San Diego virus. The animal tests permitted no official diagnosis although the slaughter and quarantine methods were again practised. Indemnification in the amount of $45,350 was made for the slaughter of 5,578 animals (2, 6).

Cross immunity tests against vesicular stomatitis virus (types Indiana and New Jersey) and foot-and-mouth disease virus (types A, O, C) showed that the San Diego virus was immunologically distinct from both these viruses. In comparing the 1932 and 1933 outbreaks, it was stated (3) that, "The true classification of the virus causing the 1932 swine outbreak of foot-and-mouth like disease must be considered as not having been definitely determined, even though a diagnosis of foot-and-mouth disease had been made and eradication carried out accordingly. It is believed, if more horses had been used in the tests, that lesions would have been produced, thus making the virus of 1932 and 1933 alike in every respect." Following the 1933 outbreak a new disease of swine was described by Traum (3) in the following statement, "Thus, we are confronted by a vesicular disease in swine, which so far has shown as much difference in experimental inoculations and immunological tests from both vesicular stomatitis and foot-and-mouth disease, as does foot-and-mouth disease from vesicular stomatitis and, although great similarity exists between the viruses of vesicular stomatitis and foot-and-mouth disease, we have been designating them as separate diseases. It therefore seems that with the information at hand the swine disease discussed above should be recognized as a new entity. Vesicular exanthema of swine is suggested as a name for this disease."

In June of 1934, 15 months after the San Diego outbreak of 1933, the disease appeared on a garbage feeding hog ranch near San Jose, California, some 500 miles distant from the San Diego foci (2, 7). During the next 3 months the infection spread over 5 counties in Central California involving 27 ranches, and four ranches in Los Angeles and San Bernardino Counties, 400 miles to the south; 31 premises and 95,000 hogs were affected. All of the cases occurred on hog ranches practising garbage feeding, and as had been the case in the 1932–33 outbreaks, only swine were involved. Virus recovered from this outbreak regularly infected swine, horses were only mildly susceptible, whereas cattle and guinea pigs were completely refractory (2).

In the absence of indemnification, the original slaughter program was not employed, but instead a rigid quarantine was imposed on infected premises until all evidence of the disease had disappeared. Trucks used for hauling garbage were disinfected upon departure, and steps were taken to insure that truck drivers and ranch attendants did not contact other hog ranches or livestock premises (2). In 1935 the disease reappeared on 4 of the premises infected in 1934 and involved about 13,000 hogs. The disease was relatively mild, and the quarantine measures were again imposed.

In 1936 the disease struck first on April 8 in San Diego County on one ranch and infected approximately 90 per cent of the animals (7). The infection did not spread to neighboring ranches but instead, on April 24, appeared in the San Francisco Bay Area, 500 miles north of San Diego. By June 20, 13 more or less widely separated premises were involved (7). No cases were reported from June 20, 1936, until December 4, 1939, despite the fact that regular inspection of garbage feeding hog ranches was carried out. Los Angeles County with the largest hog population in the state had been free of the disease for 6 years prior to March 1940 (8).

On December 4, 1939, an outbreak of vesicular exanthema was found on one garbage feeding hog ranch in San Mateo county. An immediate and rigid quarantine was imposed on the infected area. Slaughterers, commission firms and stockyard officials were ordered not to accept shipments of hogs from the infected area. This economic quarantine was relaxed only when a definite diagnosis had been made, and then only swine coming from noninfected premises could

TABLE 1

*Incidence of vesicular exanthema in California for the period 1932 to 1952, showing number and type of infected premises**

Year	Number of Outbreaks According to the Types of Premises			Number Swine Involved	Total Swine in State	Per Cent Total Swine Infected
	Garbage feeding	Grain feeding	Slaughter house			
1932	5	0	0	18,747	672,000	3
1933	3	0	0	5,533	706,000	0.7
1934	31	0	0	95,917	660,000	14.4
1935	4	0	0	10,100	530,000	2.0
1936	14	0	0	13,625	610,000	3.1
1937	0	0	0	0	732,000	0
1938	0	0	0	0	820,000	0
1939	15	0	0	32,000	763,000	0.4
1940	161	7	1	277,250	885,000	31.3
1941	155	15	0	160,104	876,000	18.0
1942	15	0	0	84,300	894,000	0.9
1943	122	3	14	288,355	1,019,000	28.0
1944	154	7	10	429,876	1,060,000	41.5
1945	58	0	2	127,620	763,000	16.7
1946	52	0	1	108,732	717,000	15.2
1947	129	10	4	212,535	664,000	32.0
1948	25	0	0	84,566	641,000	13.0
1949	101	0	4	199,875	671,000	29.8
1950	169	6	9	272,222	687,000	39.7
1951	53	1	4	82,442	653,000	12.4
1952	105	4	107	224,976	610,000	37.0
Totals..	1,371	53	156	2,739,275	12,418,000	—

* There are approximately 20,000 premises on which hogs are raised in California. Four hundred of these are garbage feeding and have a hog population of about 230,000 per annum, the remaining 19,600 are grain feeding. Modified from Duckworth (9).

be slaughtered. In addition all hogs going to slaughter from the area were individually examined (2, 7). In spite of all the quarantine efforts, 223,000 hogs, on 123 premises, located in 25 counties became infected. Within 6 months, one fourth of the state's hog population was involved.

From June to October of 1940 a respite from the disease occurred, but on October 5, 1940, the infection reappeared in 12 counties in the Central portion of the state and in December of 1940, it appeared in Los Angeles County, involving 57 permises and 54,250 additional swine. During the year 1940, 277,250 swine on 169 premises were infected. The 1940 outbreak was noted for the severity of the disease and by the fact that 7 of the foci were grain feeding ranches and one was a stockyard, marking the first time that infections were observed on nongarbage feeding premises (7).

After 1940 the recording of individual outbreaks was discontinued, in lieu of which the total number of outbreaks for any one calendar year was substituted. Since 1940 the disease has recurred each year. The number of swine infected has varied from 439,876 head in 1944 to 84,442 head in 1951. Table 1 modified from Duckworth's report (9) shows the number of outbreaks, their place of origin, and the number of swine involved per year for the first 20 year period (1932–52). Figure 1 shows the counties involved in the epizootics.

In 1948 and again in 1949, the virus appeared in a number of swine being shipped to the port of Honolulu. These animals had been loaded from California ports and, it is assumed, had come in contact with the virus prior to or during shipment. Prompt quarantine and slaughter before reaching Hawaii prevented the spread of the disease to the Hawaiian mainland. No outbreaks have ever been reported in Hawaii.

On June 16, 1952, vesicular exanthema appeared at a plant manufacturing biologicals in Grand Island, Nebraska. The source of the infection was traced to Cheyenne, Wyoming, where hogs had been fed garbage from transcontinental trains whose point of origin was California. It is assumed that contaminated pork scraps were the source of the virus. Before the disease was detected in the herd at Grand Island, some of the hogs were shipped to the Omaha stockyards, where they were in turn resold. In this manner the disease immediately fanned out and by July 29, just 43 days after discovery of

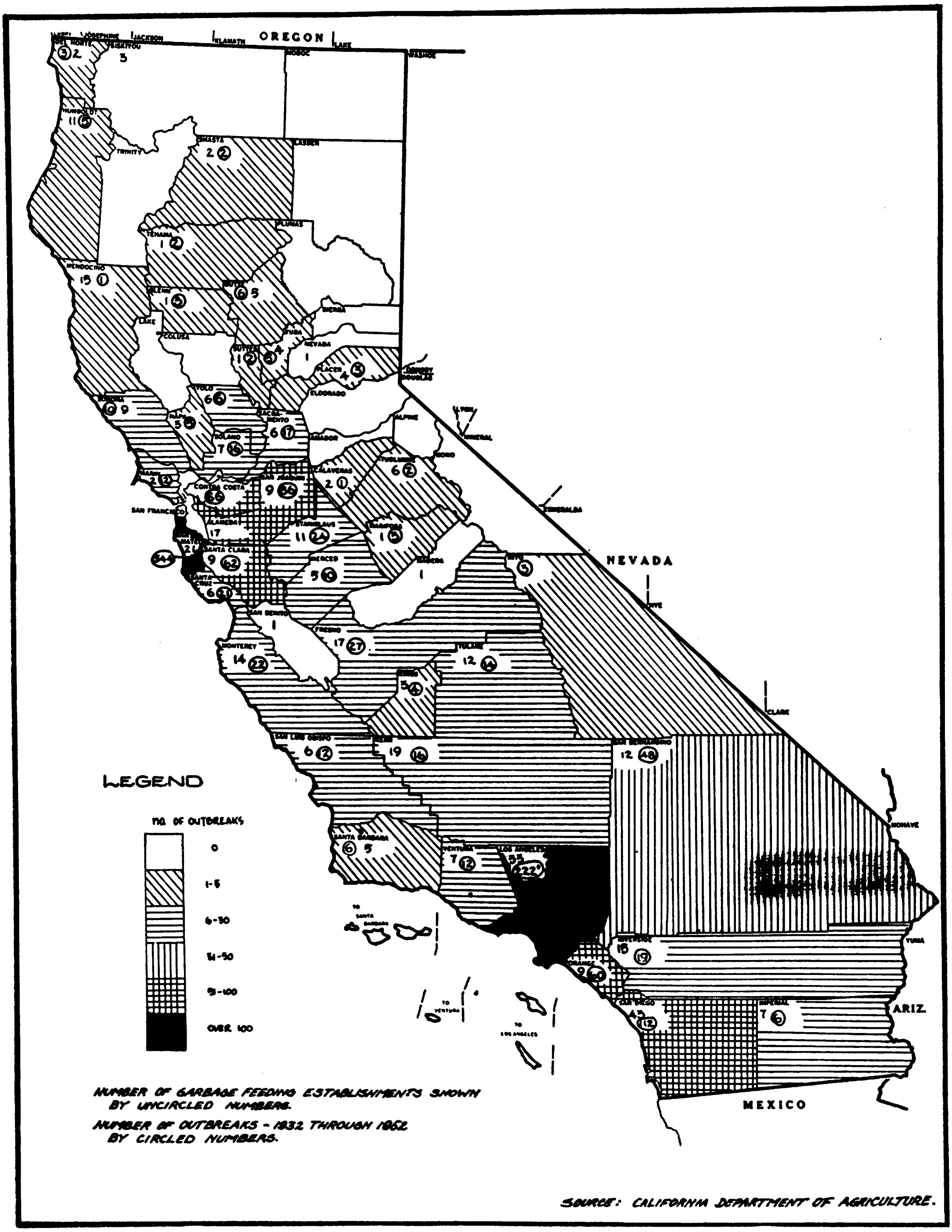

Figure 1. Outbreaks of vesicular exanthema in California, 1932 to 1952 (by counties).

the disease in Nebraska, 19 states were placed under Federal quarantine for vesicular exanthema. On August 1, 1952, a state of emergency was declared by the Secretary of Agriculture, thus providing Federal support for an active eradication program including slaughter and payment of indemnities where deemed necessary (10).

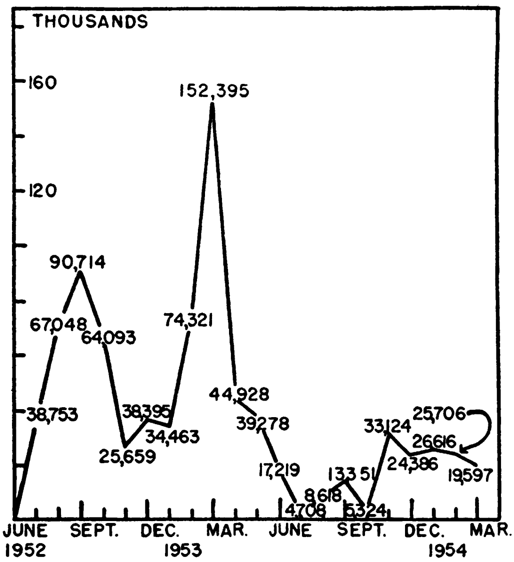

Figure 2. Number of vesicular exanthema infected-exposed swine during national outbreak.

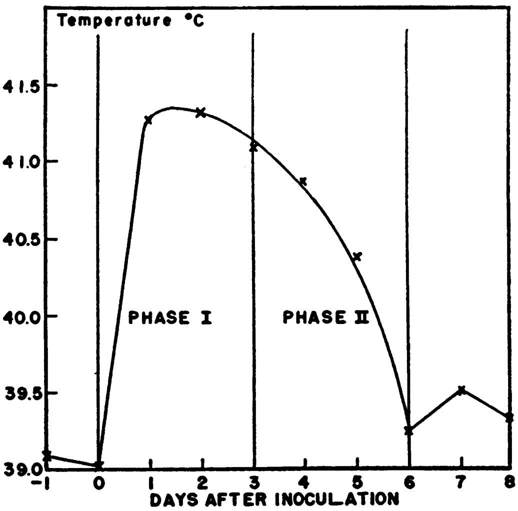

Figure 3. Characteristic temperature curve following intradermal inoculation of swine with vesicular exanthema virus.

From June, 1952, to September, 1953, a total of 42 States and the District of Columbia had experienced the disease (11). Figure 2 shows the numbers of infected-exposed swine from the period June, 1952, to February, 1954. The states of California and New Jersey are not included in these totals since the disease has become established in the raw garbage feeding areas of these states. Thus, from its initial appearance in 1932 and its apparent confinement to the state of California for 20 years, vesicular exanthema is now in a position to menace the swine industry of the entire nation to an extent that can only be assessed with the passage of time.

CLINICAL ASPECTS

Vesicular exanthema is clinically indistinguishable in swine from either foot-and-mouth disease or vesicular stomatitis (3, 12). The incubation period in both natural and experimental vesicular exanthema usually varies from 24–72 hours, with extremes from 12 hours to 12 days (13).

The introduction of virus into susceptible swine usually produces vesicles on the snout, lips, tongue and mucosae of the oral cavity and on the sole, interdigital spaces and coronary band of the foot. Occasionally lesions may appear on the teats, particularly of nursing sows (8, 14), and on the skin covering the metacarpus and metatarsus (12). Inoculation of the virus intradermally into the snout and/or mucosae of the oral cavity by needle or scarification usually produces the classical reaction, first the "primary" lesions at the site of inoculation in 12 to 48 hours and then "secondary" lesions elsewhere 48 to 72 hours later. Inoculation of the virus via the subcutaneous, intramuscular or intravenous routes is usually followed by the appearance of vesicles at any of the susceptible sites within 24 to 96 hours after inoculation.

In the typical case a diphasic symptomatologic response results. In phase 1, lasting from 48–72 hours, there is a characteristic rise in temperature (figure 3) and the appearance of primary vesicles which is usually associated with anorexia and listlessness. The primary vesicles consist of blanched, raised areas of epithelium varying from 5 to 30 mm in diameter and raised from 10 to 20 mm in height and filled with a serous fluid rich in virus. Such vesicles resemble the "blister" formation accompanying burns or excessive dermal friction. Primary vesicles follow along the original paths made by the inoculating needle. The epithelial coverings may "lift" with the slightest pressure revealing a raw, bleeding and exceedingly sensitive corium which is subsequently covered by a yellowish fibrinous membrane (12, 14, 15).

The primary lesions usually spread to involve the adjacent mucosa of the lips and cheeks. This spread is probably caused by virus liberated from the primary vesicles, as new lesions often follow the path taken by fluid escaping from ruptured vesicles. The subcutaneous tissues of the snout and tongue may become hyperemic and swollen and are sensitive to pressure. As a result the snout may appear bulbous and the swelling of the tongue lead to attacks of slobbering (8). Phase 1 is almost invariably accompanied by serious temperature changes which occasionally are as high as 108 F but more commonly between 105–106 F (16). The end of phase 1 is usually signified by a decline in temperature and rupture of the "primary" vesicles.

Phase 2 is ushered in by the formation of "secondary" vesicles on the soles of the feet, between the interdigital spaces, and at the junction of the epithelium and nail of the foot (coronary band). In all probability phase 2 corresponds with the end of the incubation period of the viremia. The initial appearance of foot lesions is usually indicated by a characteristically hesitant gait, described by field veterinarians as "ouchy". The animal may continue to walk in this halting fashion, or may simply refuse to move until the pain and swelling have decreased.

In severe attacks an edematous swelling of the legs and joints may be present. Phase 2 usually lasts for 24–72 hours following phase 1 and is terminated by the rupture of the secondary vesicles, a subsidence of pain, and the gradual resumption of normal living habits. During both phases 1 and 2, the animal may refuse food, and this, coupled with the severe pyrexia, literally "melts" the weight from market animals.

Recovery of uncomplicated cases is usually prompt and without sequellae. The healing of very severe foot lesions may result in the formation of nodules of granulation tissue which arise from the sole of the foot prior to replacement by the normal epithelium. Pyogenic bacteria may gain entrance through the damaged epithelium and cause severe and even fatal secondary infections. A certain proportion of cases lose the hoofs of the infected feet and replacement may take from 1–3 months during which time the animal may be partially lame and is constantly subject to secondary bacterial invaders. Interestingly, the junction of the old and new nail is marked by a dark brown or black line, rendering a diagnosis of vesicular exanthema infection probable even though all acute symptoms have disappeared.

In addition to the described symptoms, Hurt (8) has called attention to severe attacks of diarrhea accompanying the infection, to an apparent increase in the abortion rate of infected sows, and a general drop in milk production in lactating sows. Wicktor and Coale (17) and Mott, Patterson, Songer and Hopkins (18) observed that a mild infection may be missed completely, thus supplying a source of "occult cases".

PATHOLOGY

Lesions directly attributable to the virus, other than vesicle formation, have not been described. Histologically the vesicle consists of a circular area, "eaten" out of the stratum malpighii (Plates I–IV). The center of the area is usually devoid of anything but cellular debris and serous fluid. The first series of cells lining the area usually show cytoplasmic degeneration with pyknotic nuclei and even karyorrhexis. Cells further from the center show a ballooning of the cytoplasm, a marked stretching of the intracellular bridges and considerable intercellular edema, bordering on spongiosis. There may be a few normal epithelial cells surrounding the region of edema, but usually one vesicle tends quickly to blend into another. The subcutaneous connective tissues show acute inflammatory changes characterized by congestion, edema, hemorrhage and polymorphonuclear infiltration. In some cases where the integrity of the basement membrane has been disturbed, some of the cellular elements "spill over" into the stratum malpighii (Madin, unpublished data). Inclusion bodies have not been reported.

The pathologic changes of vesicular exanthema are very similar to those described by Chow, Hanson and McNutt (19) for vesicular stomatitis, and by Galloway and Nicolau (20) for foot-and-mouth disease.

EXPERIMENTAL HOST RANGE

Vesicular exanthema virus shows a marked predisposition to porcine epithelium and an almost equal indisposition to the tissues of other species.

Traum (3), the first to study the host range of the virus, found in the original outbreak of 1932 that inoculation of material into guinea pigs, swine and a limited number of cattle and horses produced lesions only in swine. In the 1933 outbreak inoculation of the same species provided consistent "takes" only in swine with mild reactions in 4 of 9 horses. These findings were confirmed by Reppin and Pyl (5) and Mohler (personal communication), workers who found the horse to be easier to infect than previously suspected. Crawford (15) isolated 4 strains of the virus, A, B, C, and D and found that while all 4 were infective for swine only types B and D were infectious for the horse. Crawford attempted the passage of the virus to sheep, goats, guinea pigs, white rats, white mice and hedgehogs and found that none of the 4 strains produced any visible reaction in these species. The British workers (12) using an unspecified strain infected swine, but not horses, cattle, sheep, goats, guinea pigs, rats (*Rattus norvegicus*) and hedgehogs. Madin and Traum (13) reported negative results with the chicken embryo, rabbit, and several strains of adult and suckling mice including the agouti, C57 black, hybrid black, and Namru. Man is apparently not susceptible.

Madin and Traum (13) reported that the hamster could be infected with the 1940 A and B strains if the inoculations were made intradermally over the abdomen. Reliable and clear-cut vesicles were formed at the site of inoculation within 24 hours and were accompanied by a significant pyrexia. The vesicles ruptured shortly after formation, and no further reactions were visible. Inoculation of hamsters with the current A48 and B51 strains gave completely negative results. It is presumed that sufficient differences exist among the various strains of the virus, as has already been indicated by Crawford (15), to account for the alternate failures and successes with this particular host. The current status of our knowledge regarding the hamster indicates that it does not represent a reliable small laboratory animal for study of this virus. In addition, Madin (unpublished data) failed to infect the white rat and guinea pig with the A48 and B51 strains although complement fixing antibodies were produced in the guinea pig. The ferret was also found to be refractory. Brooksby (21) has reported negative results with strains 1934 B and 1943 101 in suckling and young adult white mice. Bankowski and Wood (22) found that dogs were irregularly susceptible to types A48, B51, and C52. Intradermal-lingual inoculation produced mild lesions at the points of inoculation, characterized by erosion of the epithelium, blanching and extension. The virus was recovered from the spleen of one febrile but not from 2 afebrile animals. The present lack of a reliable laboratory host for this disease means that all work must be done in swine, and explains in part why, after approximately 20 years of work with the virus, so little is known about it.

The limited host range prompted investigations in the field of tissue culture. McClain, Madin and Andriese (23) reported the first successful cultivation of vesicular exanthema virus, demonstrating that strain B51 could be propagated on embryonic swine skin and that cytopathogenic effects were produced. Subsequently Madin and McClain (unpublished date) successfully propagated the virus on monolayer cultures of adult swine kidney and testicle following the general method used by Dulbecco and Vogt (24) and Younger (25) for the propagation of poliomyelitis virus. Bankowski and Pfeiffer (26) have propagated the B51 strain in a medium of Baker's fluid containing minced swine embryos, harvested from sows in the third to fifth week of gestation. In addition Bankowski (personal communication) claims that the virus can also be cultivated on embryonic swine skin transplanted to the chorioallantoic membrane of embryonating chicken eggs. The initial efforts in this field have made possible expanded research on vesicular exanthema virus since, for the first time, an experimental host other than live swine is available.

ETIOLOGY

Filtration of infectious, ground, vesicle covering material through gradacol membranes showed that the virus is capable of passing membranes of 44 mμ average pore diameter (APD) but not 39 mμ APD. The size of the virus is calculated to be from 13 to 20 mμ (13). Brooksby (21) reported that the 1934 B and 1943 101 strains passed gradacol membranes of 110 mμ and 70 mμ (APD) but not 37 mμ (APD). The virus has been preserved for as long as 2½ years at ordinary refrigerator temperatures in the form of unground, vesicle coverings stored in 50 per cent glycerine-phosphate buffer. It will retain its infectivity for as long as six weeks at room temperature when diluted 1–10 in 1 per cent ordinary peptone solution and will survive for at least 24 hours at 37 C in Sorensen's buffer. Storage at −10 C is routinely used (13).

In a series of feeding experiments Mott *et al.* (18) showed that infected meat scraps were infectious after storage at 7 C for 4 weeks and at −70 C for 18 weeks. Traum and White (unpublished data, 1941) placed infected vesicle coverings inside the bone marrow cavity of both cured and fresh hams, then refrigerated both overnight. Both hams were then "cooked" at 184 F under 10 lb steam pressure for 10 minutes in a garbage cooker. When the vesicle material was recovered, ground, and inoculated into test swine, it proved to be highly infectious. In certain cases where viral suspensions had lost their infectivity, Madin and Traum (13) found it possible to "reactivate" them by the addition of 1–1,000 cysteine monohydrochloride to the virus suspension. The minimum period necessary to "reactivate" was found to be 8 days, and once "reactivated", the infectivity was retained over the longest period tested, 262 days. Both Madin and Traum (13) and Mott *et al.* (18) found fresh 2 per cent lye solution to be a practical disinfectant.

The existence of a plurality of virus types was proved by Crawford (15) through his work with a series of virus collections made in 1933 and 1934. Four immunological types A, B, C, and D, based on cross immunity tests, were found in swine. Two of the types, B and D, were infectious for swine only, whereas the other two, A and C, were infectious for both horses and swine. Some difference in the severity of clinical symptoms was noted; for example, both the B and D types caused more severe reactions than either the A or C. In 1940–42, 3 immunologically distinct types were recovered in California but were subsequently lost. However, contrary to the report (13) that all of the types prior to 1948 were lost, two are still available, the 1934 B of Crawford and the 1943 101 strain collected by Traum (21). In December, 1948, Madin and Traum (13) isolated A48; in 1952 Bankowski reported the isolation of the B51 and again in 1952 the C52 and in 1953 the D53 (27, 28, 29). Brooksby (21) has recently compared the first 5 of these strains and has found them to be distinct antigenic types.

Complement fixation and serum neutralization tests corroborate the immunological identity of the types. Bankowski, Wichmann and Kummer (28) have demonstrated that the types can be separated by complement fixation even though some cross reactivity was encountered. Using their method, Brooksby (21) has confirmed these results. McClain, Madin and Andriese (23), using a different complement fixation technique, separated the A and B types. Specific serum neutralization, as observed by the failure of the virus to produce cytopathogenic effects in tissue culture in the presence of homologous serum, can also be used to differentiate the types (23).

Vesicular exanthema virus produces a viremia which apparently accounts for the formation of the "secondary vesicles". Thus, the virus may be recovered from the blood prior to 72 hours, while the spleen is positive up to 48 hours (13). In a larger series of experiments Mott *et al.* (18) slaughtered a group of inoculated swine approximately 6 hours prior to the development of vesicles (30 hours after inoculation); feeding experiments in swine using feet and snout, spleen, crushed bone, whole blood, lymph glands, viscera and muscle resulted in the production of clinical vesicular exanthema. Animals which had been fed feces and urine failed to develop a clinical infection. In the feces-fed group, however, both test swine were immune to subsequent rechallenge, thus indicating that sufficient virus had been present to stimulate immunity in these animals. It appears then that the virus quickly becomes widespread throughout the hog's body. Mott *et al.* (18) reported that the time of lesion development varied with the tissue fed and concluded that the time variation was related to the amount of virus available to the test animal. For example, the group fed feet and snout material developed lesions in 40 hours, those fed spleen or crushed bone in 72 hours, whole blood or lymph glands in 96 hours, viscera or muscle only after 6 days.

The ID_{50} of fresh vesicle covering material has been shown by Mott *et al.* (18) to be $1 \times 10^{-5.3}$ which is in close agreement with the figure of 1×10^{-6} suggested by Madin and Traum (13). Comparative titrations by various methods of exposure with infected vesicle covering material or infected defibrinated blood indicated that it takes 10 to 100 intradermal snout MID's to make one intravenous or subcutaneous MID and 100 to 1,000 intradermal snout MID's to make one MID via the oral route (18). These same authors observed that when a susceptible animal was exposed to small quantities of virus, an occult case of the disease with subsequent immunity frequently develops.

DIAGNOSIS

The diagnosis of a vesicular disease is not difficult since the clinical signs of pyrexia, vesiculation and lameness are almost invariably present. The similarity of the clinical syndrome produced by vesicular exanthema, vesicular stomatitis, and foot-and-mouth disease makes the *differential* diagnosis of a vesicular disease difficult. This

TABLE 2

Clinical response of the three vesicular viruses in the important hosts and by various routes of inoculation

Test Species	Route of Inoculation	No. Animals Needed	Responses Expected if Unknown Virus Is:		
			VE	VS	F and M
Swine	Intradermal snout, lips, plus scarified snout	2	+	+	+
	Intravenous	1	+	+	+
Horse	Intramuscular	1	∓	−	−
	Intralingual	1	±	+	−
Cow	Intradermal tongue, gum and lips	1	−	+	+
	Intramuscular	1	−	−	+
Guinea pig	Intradermal volar surface of the plantar pads	2	−	+	+

Modified from Madin and Traum (13).

+, Produces typical disease process; −, no clinical reaction; ∓, disease process rarely occurs; ±, usually very mild evidence of vesicular disease approximately 50 per cent of the time.

clinical similarity is further complicated when the outbreak occurs in swine since this animal is susceptible to all three viruses.

The present method of differentiating among vesicular exanthema, vesicular stomatitis, and foot-and-mouth disease depends on the differential susceptibility of various test animals. This system is illustrated by table 2 modified from Madin and Traum (13). Similar schemes have been advanced by Traum (3), Crawford (15) and Bankowski (30), but essentially all are the same and involve the inoculation by different routes of one or more cattle, horses, guinea pigs, and known susceptible swine with virus obtained from the outbreak in question.

The weakness of this system has been pointed out by Madin and Traum (13): "this system of animal inoculation is satisfactory as long as live virus is available, speed is not critical, typing of the individual virus is not required, and a new vesicular disease has not arisen". This weakness was clearly illustrated in the initial outbreaks of vesicular exanthema in 1932–33 when the investigators found such a system of diagnosis inadequate for reaching a clear-cut decision. Because of the drawbacks to the animal inoculation system the investigation of serological methods has received attention. In 1953 Bankowski *et al.* (28) announced the development of a complement fixation test capable of identifying and differentiating the antigenic types of vesicular exanthema virus. This test employs as antigen, vesicle-covering material obtained from an outbreak, hyperimmune swine serum and guinea pig complement. The rest of the reagents are standard. It was found that a certain degree of cross reactivity among types required that each serum be titrated with homologous antigen to determine the maximum amount of hyperimmune serum which specifically reacted with the homologous virus in the absence of cross fixation with any of the other types of vesicular exanthema virus. In addition, the high procomplementary activity of swine serum was controlled by the titration of complement in the presence of normal swine serum and each antigen employed in the test. Brooksby (21) has modified this technique by the addition of sodium polyanetholesulphonate to the swine complement to destroy the third component (C_3), thus destroying the complement enhancing effect of swine serum. These initial complement fixation techniques have had preliminary trials in the field, particularly that of Bankowski *et al.* (28), and the test has proved to be of considerable diagnostic aid in the identification of vesicular exanthema virus types (30).

Serum neutralization tests have been briefly described by McClain *et al.* (23) using tissue culture of embryonic swine skin as a test host, but such a system is as yet in its earliest developmental stage. Hemagglutination has been unsuccessful (13).

TREATMENT

No treatment is known for this disease. Certain precautions of a palliative nature may be taken, which will tend to reduce the economic losses from the infection. Weight losses can be reduced if infected animals are fed soft foods or slops entirely, if they are taken off concrete or similar hard surfaces, and if adequate amounts of clean water are kept before them at all times. Where infected animals must be maintained in crowded quarters such as during rail shipment, in feed lots, or in slaughter houses, secondary bacterial complications may be controlled by the judicious administration of antibiotics.

EPIZOOTIOLOGY

Vesicular exanthema is known to be spread by at least two methods, direct contact and the feeding of raw garbage. These two routes of infection can account for the vast majority of the outbreaks but do not clearly do so for the initial outbreaks of 1932 and 1933 and the subsequent epizootic of 1934.

Direct contact includes, for purposes of this discussion, contact with contaminated feed, water and fomites as well as contact with infected animals within the hog's particular environment. It should be pointed out that, as a group, swine live in most intimate contact, and the exchange of disease agents by either immediate or mediate contact occurs constantly. This may be the reason that vesicular exanthema shows no particular seasonal incidence inasmuch as the environment suitable to it is reasonably constant.

The work of Mott *et al.* (18) is of particular interest in the matter of direct and indirect contact infection. In their experiments, a series of susceptible swine was brought into direct contact with donor animals which had been inoculated at 12, 24, 36, 48, 72, 96, 120, 144, 192, 240 and 288 hours previously. They found that the susceptible or recipient animals contracted the disease from the pigs that had been inoculated from 12–120 hours but not from those inoculated after that time. It was reasoned that such donor animals ceased excreting virus at about 120 hours after inoculation. To prove this assumption 2 donor animals were placed in contact with two normal swine in a clean pen for 12 hours. After 12 hours, the 2 donors were withdrawn and placed in a pen with two other recipients. The process was repeated at 24, 36, 72, 96, 144 and 192 hours after inoculation of the donor animals. In each pen one of the recipient animals was scarified on the snout and feet prior to the introduction of the infected swine. The donor animals showed clinical vesicular exanthema 48 hours after inoculation. The results showed that the recipient animals were positive in the 24, 36, 48, 72 and 96 hour trials, but not in the 12, 144, and 192 hour groups. These data indicated that prior to 24 hours virus was not eliminated by the donor animals but began shortly after and continued until 96 hours after inoculation. To determine the extent of environmental exposure possible, two normal contacts were placed in each of 8 infected pens at 0, 24, 48, 72, 96, 120, 144 and 168 hours after removal of the infected swine. In the 72 hour group, one of the normal contacts developed lesions. Subsequently, it was shown by challenge with live virus that both animals in the 72 hour group had been exposed to the virus, and one in the 0 hour group. This erratic pattern of indirect exposure was similar to that found by Crawford (15).

From the earliest outbreaks until the present, it has been noted that the percentage of hogs infected on any given premises or within any given group varies considerably with the outbreak in question (7, 8). In some cases only a small percentage or only certain pens or lots would be involved, whereas in others nearly 100 per cent would be involved. The reason for such variation is not clearly understood.

What then is the role of raw garbage as a vehicle of spread? According to Duckworth (7) "Raw garbage is the source of vesicular exanthema". By this he means that the evidence gathered over a 20 year period and shown in table 1 indicates that the feeding of raw garbage is the principal vector in the spread and perpetuation of this disease. Mulhern (11) has reported that almost all of the outbreaks occurring after the 1952 "escape" of the virus from California have either had direct or indirect connection with garbage feeding establishments. The link between raw garbage and the virus is apparently infected pork scraps which act as a reservoir of the disease (2). This hypothesis gains theoretical support from the feeding experiments conducted by Mott *et al.* (18) and from the unpublished studies on the survival of the virus by Traum and White described earlier in this review. There appears to be no reason to assume from these experiments that the virus could not survive in an infected carcass and eventually find its way back to susceptible swine through raw garbage. Efforts to prevent the almost constant recurrence of the disease on raw garbage feeding ranches by cleanup and disinfection have usually met with failure. In contrast, where grain feeding ranches have been similarly treated, they have been very successful. The practice of shipping feeder stock from grain feeding ranches to be fattened on raw garbage feeding premises furnishes a continuing susceptible population for infection with virus introduced through raw garbage or residual on the garbage feeding establishment. This provides foci of infection from which the disease may be spread and lends substance to the claim that raw garbage is the source of vesicular exanthema.

Whereas this mode of spread explains many of the outbreaks, it does not necessarily explain all of them, for example, the 1932, 1933 and 1934 outbreaks. In 1932 no disease such as vesicular exanthema excepting foot-and-mouth disease had ever been reported as occurring in swine. It is particularly significant to recall that California had experienced foot-and-mouth disease in 1924 25 and again in 1929 as a result of which all regulatory officials were peculiarly attuned to "a vesicular disease outbreak". We can be reasonably certain that the 1932 outbreak was the first to occur and had its origin in one of the areas described earlier in this review. From the evidence available at that time and from a subsequent review of this evidence the outbreak in two of the areas (Orange and Los Angeles Counties) was not related to the outbreak in San Bernardino. Thus, two separate foci were apparently present almost simultaneously. The ranches in Orange and Los Angeles Counties obtained their garbage only from domestic sources by contract. The San Bernardino County premises could possibly have purchased garbage from a foreign ship through a contract with the city of Long Beach, but it is highly doubtful that any significant amount of such garbage found its way to the hog ranches. In this respect, it is important to remember that, since the 1929 outbreak of foot-and-mouth disease, a regulation had been in effect that all ships were forbidden to bring garbage into ports.

In 1933 the second outbreak occurred, this time 100 miles south of the 1932 occurrence but again on a garbage feeding hog ranch. Was there a link between the 1932–33 outbreaks? The only association outside of raw garbage was that one of the ranches involved in both the 1932–33 outbreaks belonged to the same family. There is no evidence, however, that man had been instrumental in transmitting the disease in 1933. As near as could be ascertained, the 1933 outbreak was a distinct and separate outbreak, similar to the 1932 occurrence. In 1934 the third outbreak occurred, again on a garbage feeding hog ranch 500 miles distant from the 1932–33 foci. In discussing the 1934 outbreak, Duckworth (7) pointed out that: "It is inconceivable that infective material of any kind could have carried over from either of the two earlier outbreaks and found its way into a swine herd 500 miles distant 15 to 26 months later". Also, to be remembered is that all of the animals in the 1932–33 epidemic were slaughtered and buried, and, therefore, none of the carcasses found its way into the normal trade channels and could not have contaminated raw garbage with virus. Thus, it appears that the 1934 epidemic represented yet another separate and distinct focus.

The source of the virus in the first three outbreaks is difficult to understand. Shope (personal communication) has suggested that vesicular exanthema may be primarily a disease of some "wild" animal and that domestic swine happen to be mutually susceptible. Hog ranches which feed raw garbage may serve as a food source for such a reservoir, and in the course of events swine are brought into suitable contact with the infection. No experimental evidence is at hand to support such a hypothesis at present. To further complicate an understanding of the epizootiology of the disease no outbreaks were reported during the 42 month period between June 20, 1936, and December 4, 1939. During this time all of the swine practices had been continued as usual, and contrary to the situation which prevailed in 1932, 1933, and 1934 there was contaminated pork in circulation in the trade channels since from 1934–1936 a total of 127,000 infected animals had gone to slaughter houses in the state. Thus while all the *known* means of transmitting the disease were at hand, no outbreaks were reported. Currently then, we have no satisfactory explanation as to the actual source of the virus in 1932–1934, nor are we able to explain many of the epizootiological questions concerning this disease. We can recognize, however, that vesicular exanthema represents one of the most interesting epizootiological problems in veterinary medicine.

CONTROL

The experience in California indicates that methods for adequately controlling this disease have yet to be developed. Whether such a statement is applicable to efforts to control the disease on a national scale by "stamping out" and quarantine cannot be determined at this time.

Two methods of control have been used in California, eradication and quarantine. In 1932 and 1933, the time honored methods of slaughter and thorough clean-up so successfully employed against foot-and-mouth disease in this country were applied (3), yet the disease reappeared in

1934, 400 to 500 miles distant from the first two foci. In 1934, slaughter measures were abandoned, and a quarantine of infected ranches was imposed instead (2). This quarantine consists of embargoes against moving swine from infected premises until all signs of the disease have disappeared. In addition, the movements of vehicles and men are controlled to minimize the possibility of spread by this route. After quarantine has been imposed, a differential diagnosis between foot-and-mouth disease, vesicular stomatitis and vesicular exanthema is made. In stockyards under quarantine, affected hogs are released for slaughter in accordance with the meat inspection regulations governing each vesicular disease. Duckworth (7), questioning the value of restrictive quarantine, slaughter and disinfection in California, concluded that these methods of eradication were not likely to succeed unless the disease was attacked at its source. He believes that the California quarantine, which at times was quite rigid, failed to control the spread of the infection.

In place of the rigid quarantine, which has failed to halt the disease in California, Duckworth (7), Mulhern (11), Shope, Sussman and Hendershot (31), and Duckworth and Traum (32) recommended the cessation of feeding raw garbage to swine. It is generally agreed that measures less restrictive than this will fail to control the disease at either the local or national level.

The prevalence of feeding raw garbage varies considerably from state to state and changes somewhat with the times. In 1939 Wright (33) made a survey of all cities with populations over 10,000. Replies received from 764 or 79.3 per cent of 964 such cities revealed that 296 cities disposed of their garbage by feeding it to swine, while an additional 107 cities disposed of part of their garbage in this manner. Thus a total of 403 or 52.7 per cent of the 764 cities replying disposed of municipal garbage in part by feeding it to swine. In 1949 Snyder (34) in a survey of 153 cities having a population of 10,000 or over found that only 19 (12.4 per cent) used hog feeding as a method of garbage disposal. Rawn in 1950 (35) estimated that 31 per cent of all cities in the United States with population in excess of 5,000 disposed of garbage wholly or in part by feeding it to hogs. Thus from the figures available it would appear that this method of disposing of municipal garbage is gradually being replaced by other means.

The total number of hogs fed raw garbage is estimated by the United States Department of Agriculture (36) to be slightly over 500,000 or less than 1 per cent of the country's hog population. Unfortunately, this practice is one that is concentrated along the North Atlantic seaboard states and California. In the latter state approximately 40 per cent of all slaughter hogs raised are fed garbage (37). This concentration would permit potential establishment of the disease on a more or less permanent basis and continually menaces the remainder of the hog population with a reservoir of the infection.

The control of raw garbage as a disease vector requires legislative action in the various states. This is well illustrated by the events following the outbreak of vesicular exanthema in 1952 whereupon numerous state legislatures began the preparation of bills requiring the cooking of garbage prior to its use as hog food. Stuart (personal communication) reports that as of December, 1954, all states have enacted such laws or regulations with the exception of California, Connecticut, New Jersey, New Mexico, North Dakota and Vermont. In lieu of legislation prohibiting the feeding of raw garbage, California has prohibited the movements of hogs or pork products fed raw garbage since October 1, 1954. How effectively such legislation or prohibitions will be enforced in controlling garbage borne diseases and vesicular exanthema in particular remains to be seen.

In addition to adequate control of raw garbage two other control measures remain to be developed. Passive immunization by means of immune sera has been described by Madin (38, 39) and appears to be effective against two of the antigenic types for from 2 to 3 weeks. Such a product should aid in preventing "breaks" during shipment of animals and should benefit the farmer in reducing expensive losses in baby pigs, pregnant sows and feeder stock.

The third procedure is active immunization against the infection. Madin and Traum (13) reported that preliminary trials with a formalinized vaccine made from infected epithelial coverings protected swine against direct intradermal challenge of the homologous strain for at least 6 months. They also remarked that such a vaccine would not be commercially feasible until a method of producing antigenic material in quantity was available. The report by McClain *et al.* (23) of the successful cultivation of the virus in tissue culture indicates that a vaccine may ultimately be added to the armamentarium of the regulatory official. The prophylactic use of immune sera and vaccines would have to take into account the existence of the plurality of antigenic types. Although this plurality complicates the problem of prophylaxis, it does not constitute an insurmountable obstacle. Thus, in the not too distant future a combination of intelligent and enforcible legislation against the feeding of raw garbage, accompanied by the judicious use of prophylactic agents when available, may ultimately make vesicular exanthema a manageable disease.

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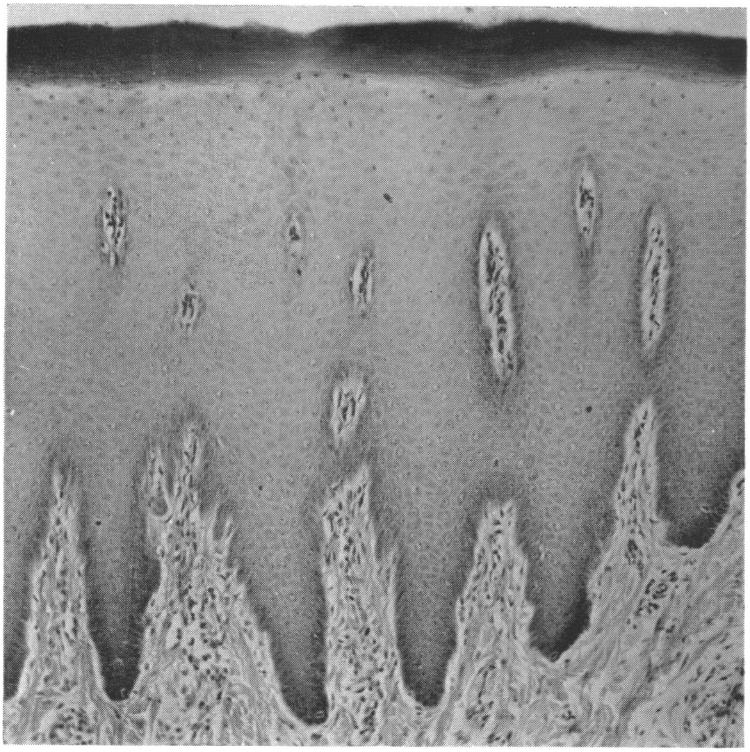

PLATE I. Normal swine snout epithelium, Giemsa (100 ×).

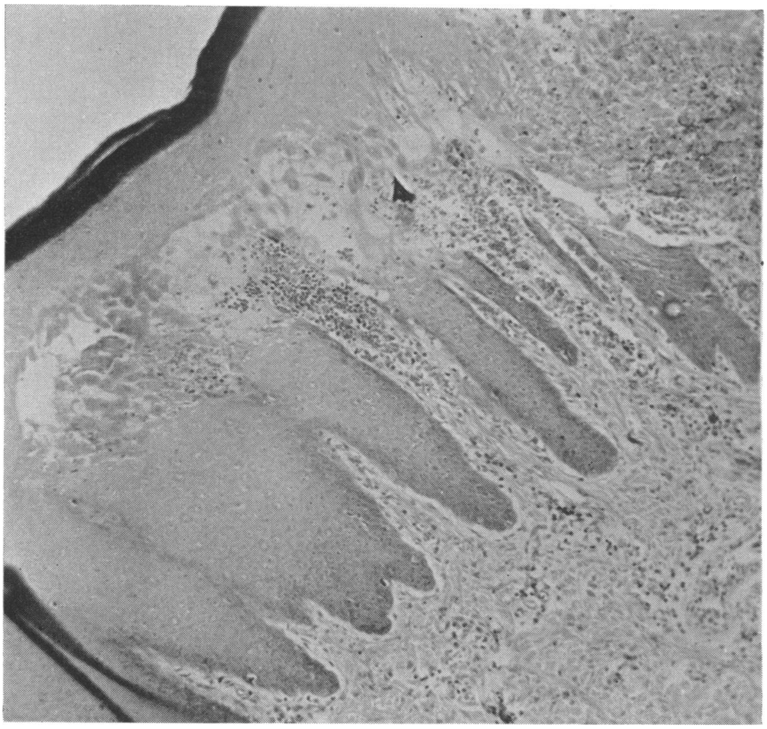

PLATE II. Vesicular exanthema infected swine snout epithelium, Giemsa (100 ×).

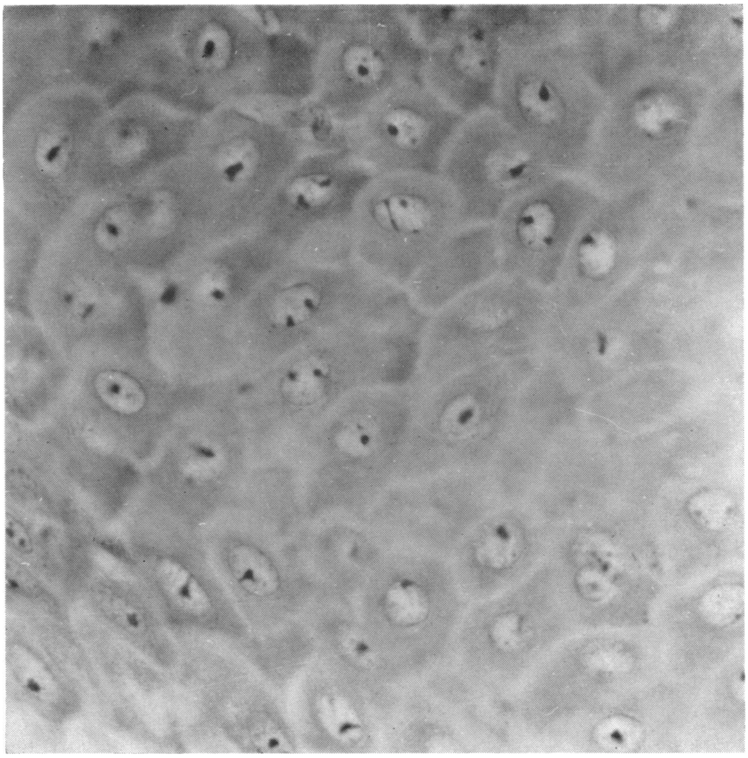

Plate III. Normal swine snout epithelium, Giemsa (1,000 ×).

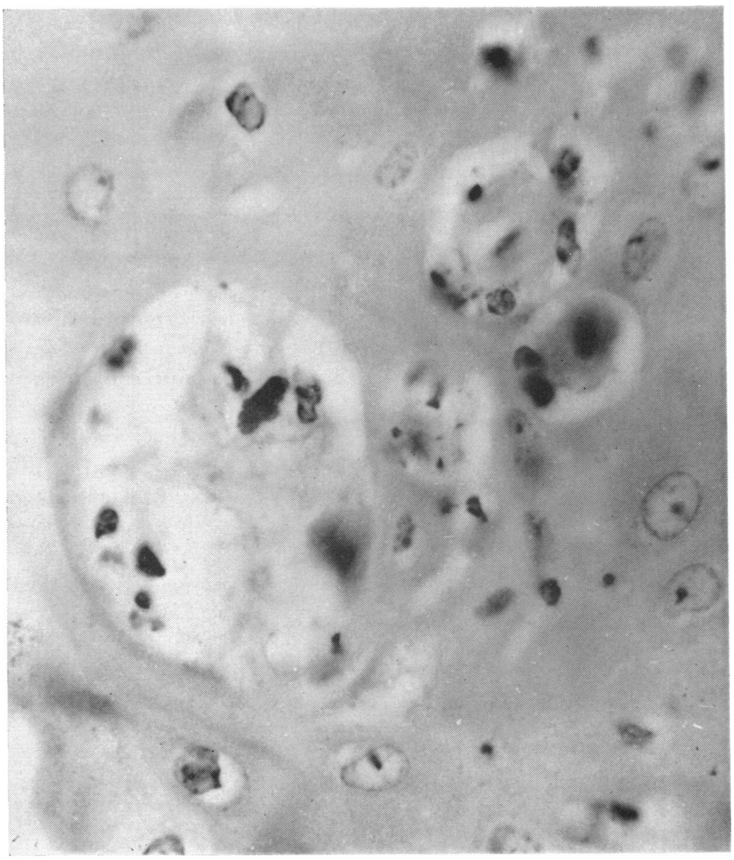

Plate IV. Vesicular exanthema infected swine snout epithelium, Giemsa (1,000 ×).